COOPER & DUNHAM LLP

ATTORNEYS AT LAW
1185 AVENUE OF THE AMERICAS, NEW YORK, NEW YORK 10036
TELEPHONE: (212) 278-0400

CHRISTOPHER C. DUNHAM
NORMAN H. ZIVIN
JOHN P. WHITE
WILLIAM C. PEUTON
ROBERT D. KATZ
DONNA A. TOBIN
RICHARD S. MILNER
RICHARD F. JAWORSKI
PAUL TENG
GARY J. GERSHIK
JASON G. MARIN
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AUDE GERSPACHER
JEFFREY C. SMISH
NARESH SRITHARAN
DAVID J. KERWICK*
TONIA A. SAYOUR

FACSIMILE: (212) 391-0525
(212) 391-0526
(212) 391-0630

OF COUNSEL
DONALD S. DOWDEN

SCIENTIFIC ADVISOR
MURIEL M. LIBERTO, PH.D.

FOUNDED 1887
www.cooperdunham.com

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DATE : December 23, 2004 **TIME:**

SERIAL NO. : 09/904,356, filed July 12, 2001 (Our Docket 43966-CB/JPW/AJD)

RE: **Communication Regarding December 7, 2004 Examiner's Interview** in connection with Graham P. Allaway et al., METHODS FOR USING RESONANCE ENERGY TRANSFER-BASED ASSAY OF HIV-1 ENVELOPE GLYCOPROTEIN-MEDIATED MEMBRANE FUSION, AND KITS FOR PRACTICING SAME, U. S. Serial No. 09/904,356, filed July 12, 2001, including a signed Facsimile Certificate of Mailing dated December 23, 2004.

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Docket No. 43966-CB/JPW/AJD

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Graham P. Allaway et al.

Serial No.: 09/904,356 Examiner: Jeffrey S. Parkin

Filed: July 12, 2001 Group Art Unit: 1648

For: METHODS FOR USING RESONANCE ENERGY TRANSFER-BASED ASSAY OF HIV-1 ENVELOPE GLYCOPROTEIN-MEDIATED MEMBRANE FUSION, AND KITS FOR PRACTICING SAME

1185 Avenue of the Americas
New York, New York 10036
December 23, 2004

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMMUNICATION REGARDING DECEMBER 7, 2004 EXAMINER'S INTERVIEW

This Communication is submitted pursuant to 37 C.F.R. 1.133(b) to make of record the substance of the discussion between Examiner Jeffrey S. Parkin and applicants during an interview held December 7, 2004 at the U.S. Patent and Trademark Office in connection with the above-identified application. In attendance at the December 7, 2004 interview were Examiner Jeffrey S. Parkin, Dr. Paul J. Maddon (one of the named inventors and Chief Executive Officer of the assignee of record, Progenics Pharmaceuticals, Inc., ("Progenics")), Dr. William C. Olson and Dr. Kathryn M. Brown of Progenics, Ashton J. Delauney, Esq., an associate in the undersigned's law firm, and the undersigned.

The Examiner provided to applicants a written Interview Summary (Form PTOL-413) at the completion of the interview, and a copy thereof was mailed to applicants on December 9, 2004. The present Communication is intended to provide further details of applicants' discussion with the Examiner and thereby complete the record concerning the issues discussed.

Before summarizing the interview, applicants wish to thank

Examiner Parkin for the courtesy extended in the interview held December 7, 2004. Applicants understand that the interview was very helpful to the Examiner and are optimistic that the subject application can now be allowed.

Introductory Statements

Applicants' undersigned representative noted that five applications were scheduled for discussion: U.S. Serial Nos. 09/904,356, filed July 12, 2001; 09/460,216, filed December 13, 1999; 09/891,062, filed June 25, 2001; 09/412,284, filed October 5, 1999; and 10/116,797, filed April 5, 2002. Prior to specifically discussing any of these five applications, applicants presented introductory remarks on the scientific background and legal concepts common to all the applications in order to provide an appropriate context for the subsequent discussion of the individual applications.

Overview of Scientific Background

Applicant Dr. Paul J. Maddon then presented an overview of the scientific background concerning the infection process by human immunodeficiency virus (HIV-1) and applicant's role in research thereon. Applicant noted that the HIV-1 infection process occurs in three stages: 1) attachment of HIV-1 through the envelope glycoprotein gp120 to a CD4 receptor on the target cell membrane; 2) fusion of the HIV-1 and target cell membranes after binding to a second receptor (CCR5); and 3) entry of viral DNA into a susceptible target cell mediated by the HIV-1 envelope glycoprotein gp41. Applicant stated that his and his group's contributions to this area of research involved, *inter alia*, the initial cloning of the CD4 gene in the early 1990's; identification of CD4 as the site of attachment for gp120; characterization of the functional distinction between

macrophage-tropic and T cell-tropic strains of HIV-1 based on their differential binding to $CD4^+$ cells; identification of CCR5 as the second cell surface receptor mediating fusion of HIV-1 to target cells; and development of a resonance energy transfer (RET) assay to study the process of fusion of macrophage-tropic HIV-1 strains to target cell membranes. It was noted that Progenics was founded, in part, to identify inhibitors of these three stages of HIV-1 infection and to develop such inhibitors as anti-HIV-1 therapeutics. Applicant emphasized the novelty of this therapeutic approach by noting that out of 20 anti-HIV drugs currently on the market, all but one target viral enzymes, e.g., reverse transcriptase and protease, the exception being (Fuzeon®; T-20) which targets viral fusion.

Overview of Legal Concepts

Applicants' undersigned representative then summarized the legal concepts applicable to the cases to be discussed.

Absence of Prior Art

The undersigned noted that because of applicants' pioneering role in the scientific research on which the instant applications were based, there was no prior art being cited in connection with any of the five applications to be discussed. The undersigned also noted that as a consequence of filing early-stage applications soon after making scientific breakthroughs, certain applications may not have had a large number of experimental examples of the inventions, and this was a factor which would be further considered in regard to the outstanding written description and enablement rejections in certain of the applications. The Examiner acknowledged that prior art was not an issue with respect to the five applications to be discussed.

Legal Standard for Enablement Rejections

The undersigned noted that the Examiner had issued rejections for an alleged lack of enablement in several of the applications. The undersigned also noted that the leading case on enablement, *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), emphasized that the legal standard for lack of enablement is a requirement for undue experimentation, i.e., experimentation that is not routine. In this context, the amount of experimentation required to practice the invention is irrelevant, the critical question being whether the experimentation required is routine. See *In re Wands*, 8 USPQ2d 1400, 1404:

> "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. (citations omitted)

The undersigned noted that *Wands* is a case involving the making of monoclonal antibodies, in which the Federal Circuit reversed an Examiner's initial non-enablement rejection that had been sustained by the Board of Patent Appeals and Interferences on the basis that, whereas considerable experimentation was required, this experimentation involved routine screening of hybridoma cell lines and hence was not undue experimentation.

The undersigned noted that the RET assay developed by applicants for identifying agents that inhibit fusion of HIV-1 to target cells is highly predictive for agents having the property of inhibiting HIV-1 fusion, and undue experimentation is not required to so identify said agents.

The undersigned acknowledged that not all agents so identified would become drugs useful in treating humans because of considerations such as toxicity and undesirable side effects. The undersigned emphasized, however, that such considerations are irrelevant to patentability and instead are the concern of the Food and Drug Administration (citing *Scott v. Finney* 32 U.S.P.Q. 2d 1115, 1120 [Fed. Cir. 1994]):

> Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA) ... Congress has given the responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe ... (citations omitted)

In addition, the undersigned reminded the Examiner that "it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts ..." *Amgen v. Chugai Pharmaceutical* 927 F.2d 1200, 1213 (Fed. Cir. 1991). The undersigned stated that he hoped to persuade the Examiner that a sufficient number of the *Wand* factors had been satisfied to establish that the specification was enabling for the inventions being claimed.

The undersigned also noted that as part of the enablement rejections, the Examiner had stated that use of the RET assay to identify fusion inhibitors does not constitute rational drug design. The undersigned agreed, noting that in the pharmaceutical industry, "rational drug design" is not the norm. Instead, the historical norm for identifying new candidate drugs is screening of large numbers of compounds. The undersigned noted that, in fact, it is only within the past ten years or so that Agouron Pharmaceuticals, Inc. (now part of Pfizer, Inc.) had successfully developed and marketed the first drug based on rational drug design.

/

The undersigned also noted that the Examiner had sometimes cited in his enablement rejections a lack of disclosure about the mechanism of action of a drug. The undersigned asserted, however, that disclosure of a mechanism is not a requirement for patentability. In response, the Examiner commented that it helps if the mechanism is disclosed, but acknowledged that disclosure of a mechanism is not required.

The undersigned also pointed to the fact that a single example of an embodiment of the invention may suffice to show enablement provided that "any gaps between the disclosures and the claim breadth could be easily bridged." *Amgen v. Hoechst* 314 F.3d 1313, 1336 (Fed. Cir. 2003). In this context, the undersigned stated that the instant applications and expert declarations previously submitted provide many examples of HIV-1 fusion inhibitors including chemokines, antibodies, and small molecules.

Examiner Must Consider Expert Declarations

The undersigned noted that in three of the applications under consideration, expert declarations had been submitted to support applicants' arguments in response to written description and enablement rejections, two each in two applications and one in the third. The undersigned emphasized that the Examiner is required to consider and give weight to these expert declarations, and if the statements therein are rejected, specific reasons have to be provided by the Examiner for rejecting them (citing M.P.E.P. §2164.05 and *In re Alton*).

> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332

> (Fed. Cir. 1991) ("expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement"); *cf. In re Alton*, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered)...
> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. (emphasis in original) M.P.E.P. §2164.05.

See also *In re Alton*, 37 U.S.P.Q.2d 1578, 1582 (Fed. Cir. 1996):

> ... the examiner's final rejection and Answer contained two errors: ... (2) the summary dismissal of the declaration, without an adequate explanation of why the declaration failed to rebut the Board's *prima facie* case of inadequate written description.

However, the undersigned noted that in many cases the Examiner had summarily dismissed applicants' declarations, seemingly on the basis of a difference of opinion between the Examiner and the declarants.

Utility of Post-Filing Date References

The undersigned further noted that in response to the enablement rejections, applicants and/or the experts who submitted declarations had cited post-filing date references demonstrating that applicants and others had used the RET assay, as disclosed in the specification, to identify inhibitors of HIV-1 fusion. The undersigned also noted that the Examiner had invariably failed to consider these references on the ground that they had been published after the application filing date. The undersigned quoted the Examiner's April 20, 2004 Office Action in connection with U.S. Serial No. 09/460,216:

> Applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. (citations omitted)

The undersigned stated that he fully agreed with this statement but noted that the post-filing date publications had not been used to show what was known at the time of filing. Rather, these publications had been submitted as evidence that the disclosures in the specification as filed are sufficient to enable a person skilled in the art to practice the invention being claimed without undue experimentation, i.e., to demonstrate that the disclosure was enabling as of the filing date. The undersigned noted that several Federal Circuit decisions confirm the utility of post-filing date references for this purpose, for example, *Gould v. Quigg* 3 U.S.P.Q.2d 1302 (Fed. Circ. 1987):

> As to the technical article, it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case, the later dated publication was not offered as evidence for this purpose. Rather, it was offered as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative. ... It was not legal error for the district court to accept the testimony of an expert who had considered a later publication in the formulation of his opinion as to whether the disclosure was enabling as of the time of the filing date of the '540 application. *Gould v. Quigg* 3 U.S.P.Q.2d 1302, 1305.

Rebuttal of *Prima Facie* Case of Non-Enablement

The undersigned noted that the initial burden is on the Examiner to make a *prima facie* case of non-enablement. The undersigned stated that applicants did not think the Examiner had made out a *prima facie* case in the applications to be discussed, but even assuming he had done so, applicants are entitled to rebut such a

prima facie case. It was noted that the Examiner is then required to respond to applicants' rebuttal with specificity. The undersigned maintained that applicants had rebutted the Examiner's findings of lack of enablement by argument and, in some instances, by filing expert declarations. The undersigned reiterated that, in response, the Examiner had not given due weight to the submitted declarations (citing M.P.E.P. §2164.05; *In re Alton*) and, contrary to *Gould v. Quigg*, had invariably dismissed evidence of enablement based on post-filing date publications.

Grouping of Applications for Discussion

The undersigned stated that U.S. Serial Nos. 09/904,356, 09/460,216, 09/891,062 and 09/412,284 would be grouped together (Group I) for discussion, separate from U.S. Serial No. 10/116,797 (Group II). The undersigned noted that the Group I applications are related in that they involve methods for inhibiting HIV-1 fusion using an agent that binds to the CCR5 coreceptor, which agent is identified by the RET assay, although CCR5 is not referred to by name in U.S. Serial Nos. 09/904,356, 09/891,062 and 09/412,284. The undersigned also stated, however, that differences observed in the inhibition of fusion of macrophage-tropic versus T cell-tropic HIV-1 strains with PM-1 target cells were later discovered by applicants to be due to binding of the inhibitor to CCR5 which is the coreceptor for macrophage-tropic HIV-1 strains.

The undersigned noted that the CCR5 coreceptor is specifically referred to in U.S. Serial No. 09/460,216, and further noted that in U.S. Serial Nos. 09/891,062 and 09/412,284, the agent is a monoclonal antibody. The undersigned noted that the Examiner had rejected the claims in these Group I applications on the grounds of inadequate written description and lack of enablement.

The undersigned noted that U.S. Serial No. 10/116,797 in Group II was separate from the Group I applications to the extent that it is a later application which discloses specific monoclonal antibodies that bind to CCR5 and inhibit HIV-1 infection. The undersigned also noted that the claimed invention is directed to reducing HIV-1 viral load in an HIV-1 infected subject and that the issues raised in this application are less complex than in the Group I applications. The undersigned stated that amended claims had been drafted in connection with U.S. Serial No. 10/116,797, which were believed to obviate the Examiner's grounds of rejection in the October 6, 2004 Office Action. In this regard, the undersigned noted that draft claims for the Examiner's consideration had been forwarded to him by facsimile and e-mail on December 6, 2004. The Examiner acknowledged that he had received these draft claims.

Discussion of the Subject Application (Serial No. 09/904,356)

The undersigned noted that claims 7-9 and 13 are pending in the subject application. The undersigned also noted that the Examiner had recently issued a November 17, 2004 Final Office Action rejecting all the claims on the basis of inadequate written description and lack of enablement. The undersigned further noted that the invention is directed to a method of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4+ cell susceptible to infection by a macrophage-tropic primary isolate of HIV-1 which comprises contacting the CD4+ cell with an agent which is capable of inhibiting fusion of HeLa-env_{JR-FL} to a PM1 cell, but not capable of inhibiting fusion of HeLa-env_{LAI} to a HeLa-CD4+ cell, so as to thereby inhibit the fusion of the macrophage-tropic primary isolate of HIV-1 to the CD4+ cell. The undersigned additionally noted that the invention provides a method for determining whether the agent is capable of inhibiting fusion of a macrophage-tropic primary isolate of HIV-1

to a CD4+ cell but not capable of inhibiting fusion of a T cell-tropic isolate of HIV-1 to a CD4+ cell.

Since applicants had not yet responded to the November 17, 2004 Final Office Action, the undersigned took the opportunity to address several points raised by the Examiner in that Office Action. First, the undersigned referred to the Examiner's remarks on page 3 of the November 17, 2004 Final Office Action, concerning rejections based on inadequate written description, that:

> [a]n applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. ... Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between function and structure, and the method of making the claimed invention. (emphasis added; citations omitted)

In response to those remarks, the undersigned asserted that the capability of the agent to inhibit fusion of HIV-1 to one type of cell but not to another is an identifying characteristic of the agent. The undersigned also asserted that the capability of the agent to bind to the target cell is a function of the agent. Further, the undersigned asserted that there is clearly a correlation between the function and identifying characteristic of the agent. Accordingly, the undersigned maintained that the written description is adequate to show that applicants were in possession of the claimed invention.

The Examiner posed a question as to which compounds, were he to go to the Sigma catalog with a listing of some 40,000 compounds, would he begin to consider as covered by the claims. The Examiner further inquired whether he should be looking at, for example, small molecules or peptides.

The undersigned responded that the subject specification teaches that by screening such 40,000 compounds in the Sigma catalog using the RET assay, one would determine which compound(s) meets (meet) the limitations of the claims.

Second, the undersigned noted that on page 4 of the November 17, 2004 Final Office Action, the Examiner stated that:

> Rationale (*sic*) drug design is facilitated by a knowledge of those regions that are critical for envelope interactions. In the absence of such information, the skilled artisan is essentially being asked to guess as to which agents or compounds might function in the desired manner.

The undersigned reiterated that rational drug design is not the norm in the development of new drugs. Moreover, the undersigned disagreed with the Examiner's statement that guesswork was required of the skilled artisan. The undersigned asserted that, on the contrary, the skilled artisan is being asked to do the RET screening assay and thereby identify which agents would function in the desired manner.

Third, the undersigned referred to the Examiner's statement on page 5 of the November 17, 2004 Final Office Action that:

> [w]hile the disclosure describes the isolation of four Mabs (PA-3, PA-5, PA-6, and PA-7) that are capable of inhibiting envelope-mediated viral cell fusion, none of these compounds were specific to either macrophage-tropic or T-cell-tropic isolates. The disclosure clearly stated (p. 60, first paragraph) that "The culture supernatants from hybridomas PA-3, PA-5, PA-6 and PA-7 inhibited fusion

between HeLa-env$_{JR-FL}$ and PM1 cells in the RET assay, and also inhibited fusion between HeLa-env$_{LAI}$ cells and certain CD4+ target cells (Table 3)." Thus the disclosure fails to identify any suitable agents with the desired properties.

In response, the undersigned asserted that, again contrary to the Examiner's statement, the data disclosed in the subject specification clearly shows that each of PA-3, PA-5, PA-6 and PA-7 inhibits fusion of HeLa-env$_{JR-FL}$ to a PM1 cell (see the specification at page 60, lines 13-16 and Table 3), but does not inhibit fusion of HeLa-env$_{LAI}$ to a HeLa-CD4+ cell (see Table 3 in the specification). The undersigned noted that this is what the claims recite. With regard to the data on differential inhibition of fusion by antibodies PA-3, PA-5, PA-6 and PA-7, the undersigned emphasized that the Examiner appeared to have not understood that it is not fusion of HeLa-env$_{LAI}$ to *any* CD4+ cell that these antibodies fail to inhibit, but rather, it is fusion to a HeLa-CD4+ cell (citing Table 3 in the specification). For the record, applicants note that the HeLa-env$_{JR-FL}$ and HeLa-env$_{LAI}$ cell lines used in the RET assay reflect the fusion activity of macrophage-tropic and T cell tropic HIV-1 strains, respectively (see the specification at, *inter alia*, page 52, lines 11-33 and pages 57-59).

In addition, the undersigned noted that the specification disclosed not only the PA-3, PA-5, PA-6 and PA-7 antibodies but also disclosed chemokines as examples of agents which meet the claim limitations (citing, for example, Table 4 in the specification).

Fourth, the undersigned cited the Examiner's statement on page 5 of the November 17, 2004 Final Office Action that "nothing in the disclosure points the skilled artisan toward any particular class of agents."

In response, the undersigned asserted that the class of agent is

result-determined, i.e., the screening assay is done and this leads to identification of the compounds. Moreover, the undersigned noted that at a minimum the specification enables peptides, i.e., a class of agents including chemokines and antibodies. The undersigned stated that, for example, applicants maintain that claim 9 (directed to the claimed method, wherein the agent is an antibody) is enabled.

The Examiner stated that the claim language is very broad and reads on *in vitro*, *in vivo* and clinical methods. The Examiner also stated that if he were a clinician, he would not want to know that thousands of compounds can be tested to identify an efficacious compound. The Examiner asked whether applicants were contending that the RET assay itself would enable a person skilled in the art to identify compounds that meet the claim language.

The undersigned responded that this is exactly what applicants contend. The undersigned asserted that there is a sound basis for extrapolating to *in vivo* efficacy from *in vitro* effectiveness. The undersigned acknowledged that the active compound would not necessarily become a drug for use in humans because of issues concerning, for example, possible side effects and the required dosages. The undersigned stated that applicants believe, however, that once a compound is identified in the *in vitro* assay, then that compound will also be effective *in vivo*.

Applicant Dr. Paul Maddon noted that monoclonal antibody PA14 is in Phase I clinical trials and that this antibody had proven to be highly effective in blocking HIV-1 infection in the SCID-hu mouse model.

The Examiner sought confirmation that PRO140 (a humanized version of monoclonal antibody PA14) is in clinical trials for inhibition

of HIV-1 infection. Dr. Maddon confirmed that PRO140 is in Phase I clinical trials and is being administered to a cohort of non-HIV-1 infected subjects to evaluate its safety, tolerability and pharmacologic profile in human subjects. Dr. Maddon also stated that Phase Ib trials involving administration of PRO140 to HIV-1 infected patients would begin early in 2005.

The Examiner stated in response that he was pleased to learn of these developments.

The undersigned maintained that the specification provides an adequate written description and an enabling disclosure of the subject invention since the claims are directed to an agent having specific, well defined characteristics which are disclosed in the specification, and the process for obtaining said agent is also taught in the specification. The undersigned emphasized that, based on the specification as filed, one skilled in the art would be able to make the claimed agent without undue experimentation. The undersigned noted that, notwithstanding that the Examiner had correctly stated elsewhere (see December 2, 2003 Final Office Action in connection with U.S. Serial No. 09/412,284, bridging paragraph of pages 5 and 6) that claims allowed in issued patents were irrelevant to the patentability of the claims under examination, it remains true that many pharmaceutical patents generically claim an agent wherein said agent is determined by an assay for inhibiting a process or reaction. In this regard, the undersigned mentioned patents which claim use of any inhibitor of an enzyme for treating a condition, for example, use of any inhibitor of phosphodiesterase for treating erectile dysfunction.

The Examiner stated that he would discuss applicants' arguments with his Supervisory Patent Examiner. The Examiner also stated that following this discussion with his supervisor, he would

provide guidance to applicants whether the claims are allowable or whether allowance would be dependent upon any further amendment(s).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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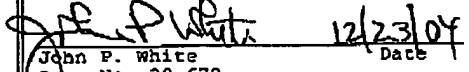

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John P. White
Reg. No. 28,678